• The prevalence of antibodies to HCV has correlated with the severity of liver disease on histologic examination.[11]

Our patient's clinical course was particularly interesting because he had the development of acute liver failure in association with newly symptomatic porphyria cutanea tarda. By self-report, our patient had a long history of three drinks of gin per day, although he said this practice had stopped three weeks before admission. He began taking acetaminophen as treatment of his abdominal discomfort. This discomfort may have represented subacute liver injury, such as from alcohol or HCV infection.

His acute liver damage at presentation was consistent with the often-overlooked syndrome of therapeutic acetaminophen hepatotoxicity in patients with chronic alcohol use: the markedly elevated AST level above 1,000 units per liter, an AST:ALT ratio of greater than 2, and a normal acetaminophen concentration in a patient taking therapeutic doses of acetaminophen.[14,15] Our patient's greatly elevated serum ferritin level may have been due to acute hepatocellular necrosis, but could have also reflected an underlying iron storage disease such as hemochromatosis. Further diagnostic testing was not possible, because the patient did not return for further evaluation.

The presence of HCV infection in this patient raises several issues. Currently available tests for HCV do not allow an accurate distinction of acute from chronic infection. Hepatitis C virus usually causes chronic liver disease[5-7]; its role in acute hepatocellular necrosis is controversial.[16-18] In this case, HCV may have contributed to a chronic liver injury, a subacute injury, or less likely, acute liver injury. The virus likely modified the hepatic milieu and perhaps the expression of porphyrins such that in a patient with acute hepatocellular necrosis (probably due to therapeutic acetaminophen toxicity), porphyria cutanea tarda became manifest.

REFERENCES

1. Dean G: The prevalence of the porphyrias. S Afr J Lab Clin Med 1963; 9:145-151

2. Felsher FF, Carpio NM, Engleking DW, Nunn AT: Decreased hepatic uroporphyrinogen decarboxylase activity in porphyria cutanea tarda. N Engl J Med 1982; 306:766-769

3. De Verneuil H, Aitken G, Nordmann Y: Familial and sporadic porphyria cutanea tarda: Two different diseases. Hum Genet 1978; 44:145-151

4. Lim HW, Cooper D: The porphyrias, *In* Sams WM, Lynch PJ (Eds): Principles and Practice of Dermatology, 1st edition. New York, NY, Churchill-Livingstone, 1990, pp 707-708

5. Lefkowitch JH, Grossman ME: Hepatic pathology in porphyria cutanea tarda. Liver 1983; 3:19-29

6. Campo E, Bruguera M, Rodés J: Are there any diagnostic histological features of porphyria cutanea tarda in liver biopsy specimens? Liver 1990; 10:185-190

7. Cortés JM, Oliva H, Paradinas FJ, Hernandez-Guío C: The pathology of the liver in porphyria cutanea tarda. Histopathology 1980; 4:471-485

8. Kushner JP, Steinmuller DP, Lee GR: The role of iron in the pathogenesis of porphyria cutanea tarda—II. Inhibition of uroporphyrinogen decarboxylase. J Clin Invest 1975; 56:661-667

9. Herrero C, Vicente A, Bruguera M, et al: Is hepatitis C virus infection a trigger of porphyria cutanea tarda? Lancet 1993; 341:788-789

10. Fargion S, Piperno A, Cappellini MD, et al: Hepatitis C virus and porphyria cutanea tarda: Evidence of a strong association. Hepatology 1992; 16:1322-1326

11. DeCastro M, Sánchez J, Herrera JF, et al: Hepatitis C virus antibodies and liver disease in patients with porphyria cutanea tarda. Hepatology 1993; 17:551-557

12. Haberman HF, Rosenberg F, Menon IA: Porphyria cutanea tarda: Comparison of cases precipitated by alcohol and estrogens. Can Med Assoc J 1975; 113:653-655

13. Cam C, Nigogosyan G: Acquired toxic porphyria cutanea tarda due to hexachlorobenzene. JAMA 1963; 183:88-91

14. Kumar S, Rex D: Failure of physicians to recognize acetaminophen hepatotoxicity in chronic alcoholics. Arch Intern Med 1991; 151:1189-1191

15. Wootton F, Lee W: Acetaminophen hepatotoxicity in the alcoholic. South Med J 1990; 83:1047-1049

16. Wright TL, Hsu H, Donegan E, et al: Hepatitis C virus not found in fulminant non-A, non-B hepatitis. Ann Intern Med 1991; 115:111-112

17. Yanagi M, Kaneko S, Unoura M, et al: Hepatitis C virus in fulminant hepatic failure. N Engl J Med 1991; 324:1895-1896

18. Wright T: Etiology of fulminant hepatic failure: Is another virus involved? Gastroenterology 1993; 104:640-643

Pulmonary Tuberculosis, Amenorrhea, and a Pelvic Mass

JOHN H. WEHNER, MD
KORINA DE BRUYNE, MD
FRANK T. KAGAWA, MD
ANTHONY C. CAMPAGNA, MD
WILLIAM A. JENSEN, MD
CARL M. KIRSCH, MD
ROGER S. ENG, MD
San Jose, California

THE WORLD HEALTH ORGANIZATION estimated that there were about 8 million new cases of tuberculosis and 2.9 million deaths from tuberculosis worldwide in 1990.[1] Furthermore, from 1985 through 1992, the number of tuberculosis cases reported in the United States has increased by 20%.[2] Infection with the human immunodeficiency virus (HIV), increased immigration from areas endemic for tuberculosis, the decline of public health institutions, and worsening socioeconomic conditions have all contributed to the national rise of tuberculosis.[2] Of the 25,701 new cases of tuberculosis diagnosed in the United States in 1990, pulmonary tuberculosis accounted for 82% of these new cases, and 5.1% of the patients had both pulmonary and extrapulmonary tuberculosis.[3] Among these cases of tuberculosis in the United States, only 399 (1.6%) involved the genitourinary tract.[3] We report a rare case of pelvic tuberculosis that developed and presented as an unusually large mass simulating pregnancy during treatment of active pulmonary tuberculosis. We also review the common clinical manifestations, diagnosis, and treatment of pelvic tuberculosis.

(Wehner JH, De Bruyne K, Kagawa FT, et al: Pulmonary tuberculosis, amenorrhea, and a pelvic mass. West J Med 1994; 161:515-518)

From the Division of Pulmonary and Critical Care Medicine, Stanford University School of Medicine, Stanford, and the Division of Respiratory and Critical Care Medicine, Santa Clara Valley Medical Center (Drs Wehner, Kagawa, Campagna, Jensen, and Kirsch), and the Department of Medicine (Dr De Bruyne) and the Department of Radiology (Dr Eng), Santa Clara Valley Medical Center, San Jose, California.

Reprint requests to Frank T. Kagawa, MD, Division of Respiratory and Critical Care Medicine, Santa Clara Valley Medical Center, 751 S Bascom Ave, San Jose, CA 95128.

ABBREVIATIONS USED IN TEXT

AFB = acid-fast bacilli
HIV = human immunodeficiency virus

Report of a Case

The patient, a 31-year-old woman, was admitted to the hospital for suspected multidrug-resistant pulmonary tuberculosis. Five years before admission, she emigrated to the United States from the Philippines and was noted to have a positive tuberculin skin test with a normal chest roentgenogram. She was given isoniazid, which she took for only three of the recommended six months. Five months before admission, she was seen by a local physician because of fever, cough without hemoptysis, anorexia, and a 12-kg (27-lb) weight loss during the preceding two months. Her chest roentgenogram revealed extensive bilateral pulmonary infiltrates. Sputum specimens were positive by smear and culture space for *Mycobacterium tuberculosis* that was sensitive to all drugs. A regimen of isoniazid, 300 mg a day; rifampin, 300 mg twice a day; and pyrazinamide, 500 mg twice a day by mouth, was started. She took only some of these medications daily for three months, in split doses, until she ran out of them a month before admission. She subsequently lost her job, and her care was transferred to a public health physician who recommended she be admitted to a hospital to rule out multidrug-resistant tuberculosis.

On admission, the patient said she did not have cough, fever, or night sweats. Her appetite was slightly improved, but she had gained only 1.4 kg (3 lb) in weight. She noted, however, that her abdomen had progressively enlarged during the previous four months and that her last menstrual period was five months before admission. Her menses had always been irregular, coming every one to two months. She had a cesarean section three years previously and had not been pregnant since then. Furthermore, she had not had sexual relations in more than two years.

On the initial physical examination, the patient was thin and afebrile. Her lungs were normal to auscultation, and examination of the heart revealed a 2/6 systolic flow murmur. The abdomen was soft, with normal bowel sounds and without hepatosplenomegaly. A large, smooth, slightly tender, nonmobile pelvic mass was palpated extending to the level of the umbilicus. The pelvic examination revealed no vaginal discharge or cervical motion tenderness. There was no peripheral lymphadenopathy.

Laboratory tests elicited the following values: leukocyte count, 16.8 × 10^9 per liter (16,800 per mm^3), with 0.76 neutrophils, 0.12 lymphocytes, 0.09 mononuclear cells, and 0.03 eosinophils; hematocrit, 0.23 (23%); urea nitrogen, 4.3 mmol per liter (12 mg per dl); and creatinine, 115 μmol per liter (1.3 mg per dl). A urinalysis showed 4 to 10 leukocytes per high-powered field, and a urine culture was negative for nontuberculous bacteria. A serum pregnancy test and an HIV antibody test were both negative. A serum CA 125 tumor-associated antigen level was mildly elevated at 44.9 U per ml (normal, 0 to 34). A repeat chest roentgenogram showed substantial improvement compared with the initial film. Magnetic resonance imaging of the pelvis revealed an extrauterine pelvic mass measuring 13.0 by 13.3 by 11.9 cm (Figure 1). Numerous fingerlike interdigitations were seen with enhancing nodular opacities extending inward from the mass wall (Figure 2). In addition, the ureters were obstructed bilaterally with secondary hydronephrosis. The right ovary was partially surrounded by the mass, and the left ovary was not visualized. There was no notable ascites or lymphadenopathy.

A sputum smear was positive and three urine specimens were negative for acid-fast bacilli (AFB). Therapy with oral isoniazid, rifampin, and pyrazinamide was restarted. In addition, because of the fear of drug resistance from her inconsistent use of antituberculosis medications, two new agents, ethambutol hydrochloride and ciprofloxacin hydrochloride, were added to what was presumably a failing drug regimen. Fine-needle aspiration of the pelvic mass revealed 4+ AFB on a smear. Because of recurrent fevers to 39°C (102.2°F) and a persistently elevated serum creatinine level to as high as 150 μmol per liter (1.7 mg per dl), a transcutaneous drainage catheter was placed in the tuberculous abscess, which drained 800

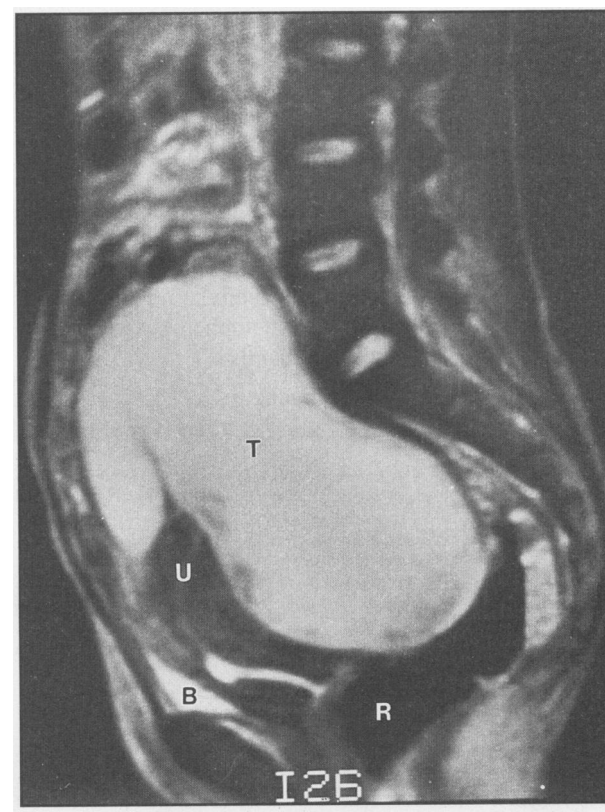

Figure 1.—A midline sagittal T2-weighted magnetic resonance imaging scan of the pelvis depicts a tuberculous abscess (**T**) that appears to originate within the pelvis and extends into the lower abdomen anterior to the uterine fundus (**U**). R = rectum, B = bladder

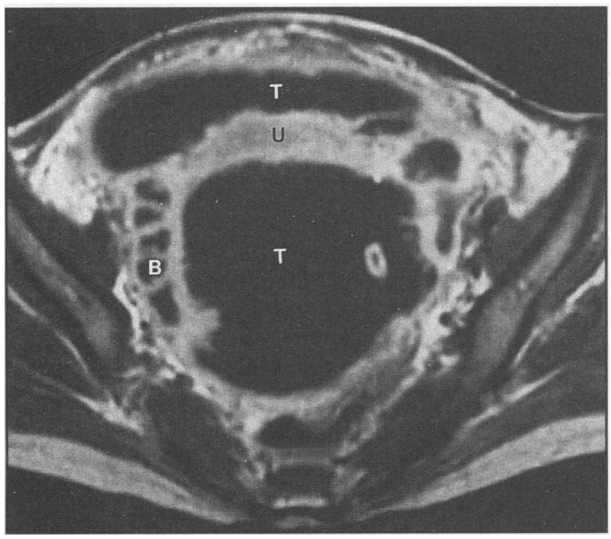

Figure 2.—A transverse, gadolinium-enhanced, T1-weighted magnetic resonance imaging scan reveals numerous fingerlike interdigitations and enhancing nodular opacities extending inward from the abscess wall. Adhesions to adjacent small bowel (**B**) are also shown. T = tuberculosis abscess, U = uterus

ml of purulent material over a six-day period. Ureteral stents were placed on both sides prophylactically for possible stricture. Thereafter, the patient defervesced and the serum creatinine level returned to normal. Finally, in view of the large AFB burden within the abscess, a third agent, capreomycin sulfate, was added until the results of a retesting of sensitivities were available.

On hospital day 24, the patient was discharged home on directly observed therapy. After eight weeks, all sputum and urine cultures, as well as the pelvic abscess culture, were negative for *M tuberculosis*. She is currently asymptomatic and has begun to menstruate.

Discussion

Genital tuberculosis is nearly always a result of dissemination from a primary source, most commonly the lungs. Infection may occur through hematogenous or lymphangitic spread, as well as direct extension from tuberculous abdominal viscera.[4] In 90% to 100% of cases, both fallopian tubes are diseased. From the diseased fallopian tubes, the tuberculous infection then spreads to the endometrium of the uterus in 50% to 60% of patients, and direct extension to the ovaries occurs in 20% to 30%. Tuberculosis of the cervix and vagina is less common.[4] Rarely, female genital tuberculosis can be acquired sexually from an infected partner with active genitourinary tuberculosis.[5] The lack of substantial ascites and abdominal adenopathy and the inability to identify the left ovary distinctly all suggest that our patient's tuberculous abscess originated from tuberculous salpingitis rather than peritoneal tuberculosis.[6]

Infertility clinics worldwide have reported an incidence of pelvic tuberculosis ranging from 1% in Australia to 19% in India, with a mean of 5% to 10%.[4] Among women of childbearing age who have active pulmonary tuberculosis, as many as 13% may have concomitant genital tuberculosis.[7] In a review in 1976 it was reported that 80% to 90% of cases of genital tuberculosis occurred in patients aged 20 to 30 years.[4] Authors have since shown an increasing incidence in women older than 40 years.[8-10]

Female patients most often present with primary or secondary infertility (13% to 55%), pelvic or abdominal pain (25% to 50%), abnormal uterine bleeding (11% to 41%), postmenopausal bleeding (2.8% to 8.4%), and amenorrhea (<2%).[4,8-10] Of 187 patients with genital tuberculosis, 11% were completely asymptomatic.[8] To our knowledge, our patient's is the largest reported mass due to genital tuberculosis and the first masquerading as a pregnancy. As in this patient, a history of tuberculosis can be obtained from 3% to 50% of patients.[4,8,10] Investigators noted that abnormal menstrual cycles, including amenorrhea, occurred frequently in patients both with and without genital tuberculosis. It was concluded that pulmonary tuberculosis indirectly affected the genital tract in most cases.[7] Physical findings can be normal in at least 43% of patients with genital tuberculosis.[10] Pelvic masses are found in 15% to 47% and are usually tubo-ovarian in origin.[7-11] Chest roentgenograms may be normal in 40% to 80% of patients with genital tuberculosis.[10,11]

Because presenting symptoms are nonspecific and are suggestive of more common nontuberculous clinical conditions—pelvic inflammatory disease, uterine fibroids, endometriosis, malignancy, ectopic pregnancy, and infertility—pelvic tuberculosis is usually not considered as a possible diagnosis. Instead, pelvic tuberculosis is often diagnosed retrospectively after specimens of extirpated tissue reveal granulomas. If, on the other hand, pelvic tuberculosis is suspected, histologic examination of specimens of premenstrual endometrial biopsies, curettage, or both may yield granulomas in 50% to 70% of patients.[4,8] Cultures of endometrium and menstrual blood may be positive for tuberculosis in 30%.[8] Repeated examinations of menstrual blood may be required, however.[12] In one report, urine cultures were positive in 18 (3.5%) of 510 patients with genital tuberculosis.[11] Diagnosis by percutaneous needle aspiration, as was done in our patient, has not been previously described.

Hysterosalpingography is usually abnormal among infertile patients with genital tuberculosis.[4,10] Although tuberculous salpingitis has characteristic radiographic findings, tubal diverticulosis, tubal endometriosis, and bacterial tubal obstruction may have similar appearances.[13,14] Thus, tissue or confirmatory cultures are recommended to establish the diagnosis of genital tuberculosis.[4]

Among patients with pelvic-adnexal masses, the serum level of the tumor-associated antigen, CA 125, has been used to help discriminate malignant from benign gynecologic conditions.[15] Although usually clinically useful as a diagnostic adjunct, reports have documented substantially elevated CA 125 levels in the serum of patients with pelvic and peritoneal tuberculosis, which declined to normal levels after treatment.[16] Our patient's mildly increased CA 125 level was probably due to genital tuberculosis.

The mainstay of treatment, as in pulmonary tuberculosis, is combination chemotherapy. Current treatment recommendations for genital tuberculosis should follow similar guidelines as for pulmonary tuberculosis.[17,18] For pansensitive organisms, a six-month course of isoniazid and rifampin combined with pyrazinamide for the initial two months should be adequate. Unless the local prevalence of isoniazid resistance is low, ethambutol should be added to the initial treatment regimen until sensitivities are known.[17-20] If isoniazid resistance is confirmed, then rifampin, ethambutol, and pyrazinamide therapy should be continued for a total of at least six months.[17] Because progressive disease developed in our patient while she was taking intermittent antituberculous therapy, three new agents—ethambutol, ciprofloxacin, and capreomycin—to which her organism was presumed susceptible, were added in accordance with the 1993 Centers for Disease Control and Prevention and American Thoracic Society recommendations for initial therapy in patients with suspected multidrug resistance.[20] In addition, all patients at risk for noncompliance or in locales with low treatment completion rates should be considered candidates for directly observed therapy.[20]

Follow-up endometrial biopsies and cultures are recommended.[11] Despite the fact that the tuberculous abscess and the sputum were smear-positive for AFB, the subsequent cultures surprisingly did not grow mycobacteria. The most likely explanation is that the organism remained sensitive to the original antituberculous regimen, as evidenced by improvement on the chest roentgenogram, and the abscess expansion was a paradoxical phenomenon, as is occasionally reported in other extrapulmonary sites of infection.[21-24]

As the drug regimens have improved, the need for surgical intervention has declined.[11] The indications for surgical treatment are persistent or recurrent pelvic pain, the development or persistence of large adnexal masses, a recurrence of endometrial infection, and a recurrence of excessive uterine bleeding.[11] A minimum six-month course of chemotherapy preoperatively has been recommended. Furthermore, the operation should completely remove the fallopian tubes, uterus, and ovaries, regardless of age.[11] In our patient, the gynecologists elected to defer a surgical procedure by placing a percutaneous drain to decompress the pelvic mass.

When medical treatment is completed, subsequent successful full-term pregnancy appears unlikely, but possible. After extensively reviewing the literature, one author concluded that in the presence of advanced disease, patients should be considered permanently infertile.[4] In a series of 84 pregnancies among 710 patients, only 35 (41%) successfully delivered. In contrast, there were 21 abortions, 26 ectopic pregnancies, and 2 neonatal deaths.[11]

REFERENCES

1. Kochi A: The global tuberculosis situation and the new control strategy of the World Health Organization. Tubercle 1991; 72:1-6

2. Centers for Disease Control and Prevention (CDC): Tuberculosis control laws—United States, 1993. MMWR 1993; 42(RR-15):1-28

3. 1990 Tuberculosis Statistics in the United States, October 1992. US Dept of Health and Human Services, Public Health Service, CDC, National Center for Prevention Services, Division of Tuberculosis Elimination, Atlanta, Ga

4. Schaefer G: Female genital tuberculosis. Clin Obstet Gynecol 1976; 19:223-239

5. Sutherland AM, Glen ES, MacFarlane JR: Transmission of genitourinary tuberculosis. Health Bull 1982; 40:87-91

6. Hulnick DH, Megibow AJ, Naidich DP, Hilton S, Cho KC, Balthazar EJ: Abdominal tuberculosis: CT evaluation. Radiology 1985; 157:199-204

7. Tripathy SN, Tripathy SN: Genital manifestation of pulmonary tuberculosis. Int J Gynaecol Obstet 1981; 19:319-326

8. Falk V, Ludviksson K, Agren G: Genital tuberculosis in women—Analysis of 187 newly diagnosed cases from 47 Swedish hospitals during the ten-year period 1968 to 1977. Am J Obstet Gynecol 1980; 138:974-977

9. Sutherland AM: The changing pattern of tuberculosis of the female genital tract—A thirty year survey. Arch Gynecol 1983; 234:95-101

10. Saracoglu OF, Mungan T, Tanzer F: Pelvic tuberculosis. Int J Gynaecol Obstet 1992; 37:115-120

11. Sutherland AM: Gynaecological tuberculosis: Analysis of a personal series of 710 cases. Aust NZ Obstet Gynaecol 1985; 25:203-207

12. Halbrecht I: Detection of latent genital tuberculosis by culture of menstrual discharge. Lancet 1947; 253:947-948

13. Siegler AM, Kontopoulos V: Female genital tuberculosis and the role of hysterosalpingography. Semin Roentgenol 1979; 14:295-304

14. Bateman BG, Nunley WC, Kitchin JD, Fechner RE: Genital tuberculosis in reproductive-age women: A report of two cases. J Reprod Med 1986; 31:287-290

15. Malkasian GD Jr, Knapp RC, Lavin PT, et al: Preoperative evaluation of serum CA 125 levels in premenopausal and postmenopausal patients with pelvic masses: Discrimination of benign from malignant disease. Am J Obstet Gynecol 1988; 159:341-346

16. Gürgan T, Zeyneloğlu H, Urman B, Develioğlu O, Yarali H: Pelvic-peritoneal tuberculosis with elevated serum and peritoneal fluid Ca-125 levels—A report of two cases. Gynecol Obstet Invest 1993; 53:60-61

17. American Thoracic Society: Treatment of tuberculosis and tuberculosis infection in adults and children. Am J Respir Crit Care Med 1994; 149:1359-1374

18. Barnes PF, Barrows SA: Tuberculosis in the 1990s. Ann Intern Med 1993; 119:400-410

19. Davidson PT: Drug resistance and the selection of therapy for tuberculosis. Am Rev Respir Dis 1987; 136:255-257

20. CDC: Initial therapy for tuberculosis in the era of multidrug resistance. MMWR 1993; 42(RR-7):1-8

21. Campbell IA, Dyson AJ: Lymph node tuberculosis: A comparison of various methods of treatment. Tubercle 1977; 58:171-179

22. Chambers ST, Hendrickse WA, Record C, Rudge P, Smith H: Paradoxical expansion of intracranial tuberculomas during chemotherapy. Lancet 1984; 2:181-184

23. Prakash B, Mehta G, Gondal R, Kumar S, Malhotra V: Tuberculous abscess of the brain stem. Surg Neurol 1989; 32:445-448

24. Muradali D, Gold WL, Vellend H, Becker E: Multifocal osteoarticular tuberculosis: Report of four cases and review of management. Clin Infect Dis 1993; 17:204-209